PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/20, 47/44 — A1

(11) International Publication Number: WO 00/04897

(43) International Publication Date: 3 February 2000 (03.02.00)

(21) International Application Number: PCT/AU99/00585

(22) International Filing Date: 20 July 1999 (20.07.99)

(30) Priority Data:

PP 4730	20 July 1998 (20.07.98)	AU
PP 4731	20 July 1998 (20.07.98)	AU
PQ 0324	13 May 1999 (13.05.99)	AU

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(71) Applicant *(for all designated States except US)*: PEPTECH LIMITED [AU/AU]; 35–41 Waterloo Road, North Ryde, NSW 2113 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TRIGG, Timothy, Elliot [AU/AU]; 8 Yosefa Avenue, Warrawee, NSW 2074 (AU). WALSH, John, Desmond [AU/AU]; 5 Stirgess Avenue, Curl Curl, NSW 2096 (AU). RATHJEN, Deborah, Ann [AU/AU]; 4 Eddy Street, Thornleigh, NSW 2120 (AU).

(74) Agent: F.B. RICE & CO.; 605 Darling Street, Balmain, NSW 2041 (AU).

(54) Title: BIOIMPLANT FORMULATION

(57) Abstract

A pharmaceutical and/or veterinary formulation comprising about 2–30 % (w/w) (on an active basis) of at least one active agent, about 0.5–20.0 % (w/w) of a pore–forming agent and the balance stearin. Such formulations provide sustained release of the at least one active agent in humans and other animals for periods of 7 days up to about 2 years.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00585

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]:

A61K 31/20, 47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT; .. Glyceryl tristearate; Stearin; excipient; Lecithin
CAPLUS;

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/08623 (F Hoffman-La Roche) 28 April 1994	1-40
Y	WO 97/00693 (Peptide Technology Limited) 9 January 1997	1-40
Y	US 4578391 (Yamanouchi Pharmaceutical Co.) 25 March 1986	1-40

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" Document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	- 5 NOV 1999
Name and mailing address of the ISA/AU	**Authorized officer**
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	A. WILCOX Telephone No.: (02) 6283 2243

Form PCT/ISA/210 (second sheet) (July 1998) COPSAA

INTERNATIONAL SEARCH REPORT

International application No. PCT/AU 99/00585

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5179079 (Novo Nordisk A/S) 12 January 1993	1-40

INTERNATIONAL SEARCH REPORT

Patent Document Cited in Search Report		Patent Family Member					
WO	94/08623	AU	51110/93	CA	2125784	EP	620740
		NZ	256413	US	5863549		
WO	97/00693	AU	59927/96	CA	2225796	EP	871467
		US	5925619	AU	18438/99		
US	4578391	DE	3301638	FR	2519864	AU	18438/99
US	5179079	AU	10858/88	CA	1326210	EP	272097
		NZ	222907	US	5179079	WO	8804556

CONTINUED

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 91755	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/AU 99/00585	International filing date *(day/month/year)* 20 July 1999	(Earliest) Priority Date *(day/month/year)* 20 July 1998

Applicant
1. PEPTECH LIMITED

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **5** sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,
[X] the text is approved as submitted by the applicant.
[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
[X] the text is approved as submitted by the applicant
[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.
[ ] as suggested by the applicant.
[ ] because the applicant failed to suggest a figure
[ ] because this figure better characterizes the invention
[X] None of the figures

IN[redacted]IONAL SEARCH REPORT

International Application No.
PCT/AU 99/00585

Box 1 Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

I[redacted]ATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00585

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 30/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT; .. Glyceryl tristearate; Stearin; excipient; Lecithin
CAPLUS:

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/08623 (F Hoffman-La Roche) 28 April 1994	1-40
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Y	US 4578391 (Yamanouchi Pharmaceutical Co.) 25 March 1986	1-40

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	- 5 NOV 1999

Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	A. WILCOX Telephone No.: (02) 6283 2243

INT[redacted]ONAL SEARCH REPORT

International application No.
PCT/AU 99/00585

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5179079 (Novo Nordisk A/S) 12 January 1993	1-40

Patent Document Cited in Search Report		Patent Family Member					
WO	94/08623	AU	51110/93	CA	2125784	EP	620740
		NZ	256413	US	5863549		
WO	97/00693	AU	59927/96	CA	2225796	EP	871467
		US	5925619	AU	18438/99		
US	4578391	DE	3301638	FR	2519864	AU	18438/99
US	5179079	AU	10858/88	CA	1326210	EP	272097
		NZ	222907	US	5179079	WO	8804556

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

CORRECTED VERSION

RECD 18 JUL 2000

WIPO

Applicant's or agent's file reference 91755	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU99/00585**	International filing date *(day/month/year)* 20 July 1999	Priority Date *(day/month/year)* 20 July 1998
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 31/29; 47/44		
Applicant PEPTECH LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand 15 February 2000	Date of completion of the report 24 May 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **A. WILCOX** Telephone No. (02) 6283 2243

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU99/00585

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

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[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-40**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-40**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-40**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

Citations

(a). US 4578391 (Yamanouchi Pharmaceutical Co.,) 25 March 1986;

(b) US 5179079 (Novo Nordisk A/S) 12 January 1993;

(c) WO 94/08623 (F. Hoffmann-La Roche) 28 April 1994

(d) GB 2052258 (Syntex (USA.) Inc.) 21 January 1981.

Explanations

Claims 1-40 are considered to be both novel and inventive when compared with the publications listed above which were cited in the International Search Report. The attorney has stated in the response filed 19 May 2000 that the claimed formulations are novel because the proportions of active agents ensure that the formulation is solid at physiological temperatures (e.g. 37°C). Citations (a) - (d) disclose fluid or gel formulations and do not anticipate a claim to a solid formulation.

The examples are directed to compositions which include the following essential features:-

-an active agent,

-lysine, sodium sulphate, hydroxy propyl methyl cellulose, glucose, sodium acetate as pore forming agents,

-stearin.

Such formulations have been shown to have sustained release properties.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
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in its capacity as elected Office

Date of mailing (day/month/year) 16 March 2000 (16.03.00)	
International application No. PCT/AU99/00585	**Applicant's or agent's file reference** 91755
International filing date (day/month/year) 20 July 1999 (20.07.99)	**Priority date** (day/month/year) 20 July 1998 (20.07.98)
Applicant TRIGG, Timothy, Elliot et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 February 2000 (15.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/20, 47/44 — A1

(11) International Publication Number: **WO 00/04897**

(43) International Publication Date: 3 February 2000 (03.02.00)

(21) International Application Number: PCT/AU99/00585

(22) International Filing Date: 20 July 1999 (20.07.99)

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PP 4730	20 July 1998 (20.07.98)	AU
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(71) Applicant *(for all designated States except US)*: PEPTECH LIMITED [AU/AU]; 35–41 Waterloo Road, North Ryde, NSW 2113 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TRIGG, Timothy, Elliot [AU/AU]; 8 Yosefa Avenue, Warrawee, NSW 2074 (AU). WALSH, John, Desmond [AU/AU]; 5 Stirgess Avenue, Curl Curl, NSW 2096 (AU). RATHJEN, Deborah, Ann [AU/AU]; 4 Eddy Street, Thornleigh, NSW 2120 (AU).

(74) Agent: F.B. RICE & CO.; 605 Darling Street, Balmain, NSW 2041 (AU).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BIOIMPLANT FORMULATION

(57) Abstract

A pharmaceutical and/or veterinary formulation comprising about 2–30 % (w/w) (on an active basis) of at least one active agent, about 0.5–20.0 % (w/w) of a pore–forming agent and the balance stearin. Such formulations provide sustained release of the at least one active agent in humans and other animals for periods of 7 days up to about 2 years.

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CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

BIOIMPLANT FORMULATION

Field of the Invention:

The present invention relates to pharmaceutical and/or veterinary formulations for the sustained release of at least one active agent. Preferred active agents include gonadotropin-releasing hormone (GnRH) agonists (e.g. deslorelin), GnRH antagonists (e.g. cetrorelix), somatostatin analogues (e.g. somatostatin-14 and octreotide), lipid lowering agents (e.g. simvastatin), cyclosporins (e.g. cyclosporin A), angiotensin converting-enzyme inhibitors (e.g. captopril), calcitonins, substance P antagonists, painkillers (e.g. morphine), opioid antagonists (e.g. naltrexone), anti-depressants (e.g. venlafaxine) and non-steroidal anti-inflammatory agents (e.g. naproxen sodium).

Background of the Invention:

For reasons including improved efficacy of action and reduced frequency of administration, there is considerable interest in the development of pharmaceutical and veterinary formulations capable of controllably releasing active agents for sustained periods (e.g. up to 6 months or more). Types of pharmaceutical agents that would particularly benefit from the development of such formulations are those which are typically administered by patients themselves over long periods (e.g. insulin for diabetes treatment, and gonadotropin-releasing hormone (GnRH) agonists for reproductive control and treatment of sex hormone-dependent diseases and conditions) and require high levels of patient compliance. In the veterinary context, sustained release formulations would reduce the stress often caused to the animal and veterinarian/owner alike by the need for repeated administration of active agents.

The present applicant's have found that sustained release of at least one active agent in humans and other animals for periods of 7 days up to about 2 years, can be achieved by using a solid formulation comprising stearin as an excipient in combination with a substance which, while not wishing to be bound by theory, appears to form pores and/or cracks in the excipient to enable the release of the active agent(s).

Summary of the Invention:

Thus, in a first aspect, the present invention provides a pharmaceutical and/or veterinary formulation comprising about 2-30% (w/w) (on an active basis) of at least one active agent, about 0.5-20.0% (w/w) of a pore-forming agent and the balance stearin.

In a preferred embodiment, the formulation comprises about 5-10% (w/w) (on an active basis) of at least one active agent, about 1.0-10.0% (w/w) of a pore-forming agent and the balance stearin.

In a more preferred embodiment, the formulation comprises about 5-10% (w/w) (on an active basis) of at least one active agent, about 2.0-5.0% (w/w) of a pore-forming agent and the balance stearin.

In a second aspect, the present invention provides a method of treating a disease or condition in a human or other animal, the method comprising administering to the human or other animal the formulation of the first aspect of the invention.

Detailed disclosure of the Invention:

The at least one active agent utilised in the formulation of the present invention, may be selected from agents having pharmaceutical or veterinary significance and may be any or a combination of peptides (e.g. hormones and antigens), polypeptides and proteins, and nucleic acid compounds and derivatives such as DNA and RNA.

Preferred active agents include:

(1) GnRH agonists

Particularly preferred GnRH peptide agonists are deslorelin (described in US4218439), eulexin (described in FR7923545, WO 86/01105 and PT100899), goserelin (described in US4100274, US4128638, GB9112859 and GB9112825), leuprolide (described in US4490291, US3972859, US4008209, US4005063, DE2509783 and US4992421), dioxalan derivatives such as are described in EP 413209, triptorelin (described in US4010125, US4018726, US4024121, EP 364819 and US5258492), meterelin (described in EP 23904), buserelin (described in US4003884, US4118483 and US4275001), histrelin (described in EP217659), nafarelin (described in US4234571, WO93/15722 and EP52510), lutrelin (described in US4089946), leuprorelin (described in Plosker *et al.*, Drugs 48 930-967, 1994) and LHRH analogues such as are described in EP181236, US4608251, US4656247, US4642332, US4010149,

US3992365 and US4010149. The disclosures of each the patent specifications and papers referred to above are incorporated herein by reference.

The most preferred GnRH agonists are goserelin, deslorelin, leuprorelin, triptorelin, meterelin, buserelin, histrelin, nafarelin and combinations thereof. The formulae of these compounds are provided below:

Goserelin	$C_{59}H_{84}N_{18}O_{14}C_2H_4O_2$ D-Ser(Bu^t)^{6}Azgly^{10}-LHRH Acetate 3-[5-oxo-L-prolyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-O-tert-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl] cabazamide acetate.
Deslorelin	6-D-tryptophan-9-(N-ethyl-L prolinamide)-10-deglycinamide P Glutamine-Histidine-Tryptophan-Serine-Tyrosine-D Tryptophan-Leucine-Arginine-Proline-ethylamide.
Leuprorelin	$C_{59}H_{84}N_{16}O_{12}$, $C_2H_4O_2$ Leuprorelin Acetate 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.
Triptorelin	$C_{59}H_{84}N_{16}O_{12}$, $C_2H_4O_2$ D-Trp^6-LHRH 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide.
Meterelin	Des Gly^{10}-2-methyl-D-Trp^6-Pro-ethyl-amide^9 LHRH.
Buserelin	$C_{60}H_{86}N_{16}O_{13}$, $C_2H_4O_2$ D-Ser(Bu^t)^6-Pro9-NEt LHRH Acetate Oxo-L-prolyl-L-histidyl L-tryptophyl-L-seryl-L-tyrosyl-O-tert-butyl-D-seryl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate.
Histrelin	Pro-His-Trp-Ser-Tyr-Leu-D(N-benzyl) His-Arg-Pro-N-ethylamide.
Nafarelin	$C_{66}H_{83}N_{17}O_{13}$, $xC_2H_4O_2yH_2O$Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-N-ethyl-L-prolylglycinaminde acetate hydrate.

Formulations according to the invention which include a GnRH agonist as the at least one active agent may be used for controlling reproductive function or for the treatment of any disease or condition wherein reduction of sex hormone (i.e. testosterone or estradiol) levels over a prolonged period is beneficial. Examples include prostrate cancer, ovarian and breast cancer, benign hormone-dependent disorders such as endometriosis, myoma and premenstrual tension, uterine fibroids, induction of endometrial atrophy prior to surgery, suppression of germ cell activity in chemotherapy, hirsutism, cyclic auditory dysfunction, porphyria and precocious puberty in children, benign prostatic hypertension in dogs and for use in other conditions where castration is known to have a beneficial clinical effect, including restoration of T cell-mediated immunity.

(2) GnRH antagonists

Particularly preferred GnRH antagonists are ramorelix (L-prolone,1-(N2-(N-(N-(N-(N-(N-(N-(N-acetyl-3-(2-naphhthalenyl)-D-alanyl)-4-chloro-D-phenylalanyl)-D-tryptophyl)-L-seryl)-L-tyrosyl-O-(6-deoxy-alpha-L-mannopyranosyl)-D-seryl)-L-leucyl)-L-arginyl)-2-(aminoacrbonyl) hyrazide, teverelix (D-alaninamide,N-acetyl-3-(2-naphthalenyl)-D-alayl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N6-(aminocarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl, cetrorelix (D-Alaninamode, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl, ganirelix (N-Ac-D-Nal,D-pCl-Phe,D-Pal,DhArg(Et)2,hArg(Et)2,D-Ala) GnRH, alanex, abarelix (D-Alaninamide,N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparainyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl; N-(S)-tetrahydrofuroyl-Gly-D2Nal-D4Ciphe-D3Pal-Ser-NmeTyr-D-lys(Nic)-Leu-Lys(Isp)-Pro-D-Ala-NH2; isopropyl-13-(N-benzyl-N-methaminomethyl)-7-(2,6-diflurobenzyl)-4,7-dihydro-2-(4-isobutyrylaminophenyl)-4-oxothieno(2,3-b)pyridine-5-carboxyatehydrochloride). Other preferred GnRH antagonists are described in US5110904, US5300492, US5807983, US5169932, US5296468 and US5502035.

(3) Somatostatin analogues

Particularly preferred somatostatin analogues include somatostatin-14, octreotide, lanreotide and angiopeptin cyclopeptides (US5569647).

Formulations according to the invention which include a somatostatin analogue as the at least one active agent may be used for treating, for example, hyperinsulinaemia and peptic ulcers.

(4) Lipid lowering agents

Particularly preferred lipid lowering agents include compounds which inhibit HMG CoA reductase such as cerevastatin, mevastatin, simvastatin, pravastatin and lovastatin.

Formulations according to the invention which includes these agents may be used for treating, for example, hyperlipoproteineamia.

(5) Cyclosporins

Preferred cyclosporins include naturally occurring cyclosporins (e.g. as described by Dreyfuss *et al.*, (1976) Europ. J. Appl. Microbiol. Vol. 3: 125-133), and analogues (e.g. as described by Wenger R.M. (1982), Chemistry of Cyclosporin A in "Cyclosporin "A", White D.G.G. ed., Amsterdam; Elsevier).

Formulations according to the invention which include a cyclosporin or cyclosporin analogue as the at least one active agent may be used, for example, as immunosuppressive agents for prophylaxis and treatment of organ rejection in allogeneic transplants.

(6) Angiotensin converting enzyme inhibitors

Preferred ACE inhibitors include captopril, enalapril, trandolaprilate, perindoprilate, quinaprilate, fasidotril, omapatrilate and lisinopril.

Formulations according to the invention which include such agents may be used, for example, as antihypertensives.

(7) Calcitonins

Preferred calcitonins include human, salmon, and porcine calcitonin. Analogues of these polypeptides may also be suitable.

Formulations according to the invention which include calcitonin or calcitonin analogues may be used for treatment of, for example, hypercalcemia and for decreasing concentrations of phosphate in patients suffering from hyperparathyroidism, vitamin D intoxication, and osteolytic bone metastases.

(8) Substance P antagonists

Preferred substance P antagonists include fragment 4-11 (i.e. Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2 and variant forms), fragment 5-11 (i.e. Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2 and variant forms), fragment 6-11 (i.e. Gln-Phe-Phe-Gly-Leu-Met-NH_2 and variant forms), fragment 7-11 (i.e. Phe-Phe-

Gly-Leu-Met-NH_2), fragment 8-11 (i.e. Phe-Gly-Leu-Met-NH_2) and fragment 9-11 (i.e. Gly-Leu-Met-NH_2). Other suitable substance P antagonists include those described in the present applicant's co-pending Australian Provisional Patent Application No. PP9008.

Formulations according to the invention which include substance P antagonists may be used for treatment of cancer including chemotherapy-induced nausea and vomiting, pain, allergy, asthma, inflammatory conditions including inflammatory bowel disease and depression.

(9) Painkillers

Preferred painkillers include opioids such as morphine, levorphanol and meperidine (pethidine), and amide local anaesthetics such as bupivacaine, lidocaine, etidocaine and mepivacaine.

Formulations according to the invention which include such painkilling agents may be used to treat acute pain (e.g. such as that experienced by hip replacement patients) or chronic regional pain.

(10) Opioid antagonists

Preferred opioid antagonists include naltrexone, naloxone and methadone.

Formulations according to the invention which include opioid antagonists may be used for treatment of opioid dependency.

(11) Anti-depressants

Preferred anti-depressants include venlafaxine, trifluprornazine, methotrimeprazine, promethazine, buspirone, gepirone and fluoxetine (Prozac).

(12) Non-steroidal anti-inflammatory agents

Preferred non-steroidal anti-inflammatory agents include naproxen sodium indomethacin, sulindac, tolmelin, acemetacin, zomepirac, mefenamic acid, fenoprofen, flufenamic acid, phenylbutazone, flurbiprofen, ketoprofen and axsain.

Formulations according to the invention which include non-steroidal anti-inflammatory agents may be used for the treatment of post-operative inflammation and inflammation associated with, for example, rheumatoid arthritis.

(13) Miscellaneous

Other suitable active agents include paroxetine for treatment of social anxiety disorder/social phobia, galanin antagonists such as galanin fragment 1-13-Pro-Pro-Ala-Leu-Ala-Leu-Ala amide and galanin (1-13)-spantide 1 for treatment of obesity, eating disorders, depression and pain; activin and inhibin fragments such as α-subunit fragment 1-32 and β-fragment 67-94 for fertility control; adrenocorticotropic hormone (ACTH) and variants and fragments for treatment of West Syndrome and infantile spasms; growth hormone and its analogues for replacement therapy in growth-hormone deficient children; erythropoietin (EPO) and its analogues for treatment of anaemia; endothelin antagonists for prevention of congestive heart failure, prevention of acute renal failure and subarachnoid haemorrhage, prevention and treatment of atherosclerosis, treatment of hypertension, prevention of stroke and treatment of chronic obstructive pulmonary disease; leptin and its agonists and antagonists for treatment of obesity and eating disorders such as anorexia nervosa, and for weight loss; thyrotropin releasing hormone (TRH) and its analogues (e.g. pGlu-His-Pro-Gly) for treatment of, for example, epilepsy; and theophylline and its analogues for the treatment of asthma, systemic capillary leak syndrome and Parkinson's disease. Vaccine antigens, including DNA encoding vaccine antigens, may also be delivered in a formulation according to the present invention.

Formulations according to the invention may include a combination of active agents. Examples of preferred combinations (comprising "Agent 1" and "Agent 2") are shown in Table 1.

Table 1:

Agent 1	Agent 2
HMG Co A reductase inhibitor	Gemfibrozil
Non-steroidal anti-inflammatory agent	Mycophenolate mofelil
GnRH agonist	Trk tyrosine inhibitor
GnRH agonist	Testosterone
Calcitonin	Estrogen
Calcitonin	Etridonate
Calcitonin	Pamridonate
Octreotide	α-interferon
Octreotide	IGF-1
Octreotide	Miclodrine
GnRH agonist	Flutamide
Etofylline	Theophylline

Preferably, the at least one active agent is/are of low to moderate lipophilicity. More preferably, at least one active agent has a log octanol/water partition coefficient (log P) (Ruelle and Kesselring (1998), J Pharm Sci. Vol. 87:1115-24) in the range of 5.0 to -3.0. Most preferred are active agents having a log P value in the range of 3.0 to -3.0 and, particularly, those having a log P value in the range of 1.0 to -3.0.

Log P values for representatives of the abovementioned classes of active agents are provided in Table 2.

Table 2:

Agent	log octanol/water partition (log P)
octreotide	1.40
cyclosporin A	2.90
captopril	-1.86
trandolaprilate	1.02
perindoprilate	-0.36
quinaprilate	0.69
morphine	0.76
lidocaine	2.26
methadone	3.93
promethazine	4.75
indomethacin	4.27
flufenamic acid	1.14
phenylbutazone	3.16
theophylline	-0.02
etofylline	0.35
TRH	-2.40

The pore-forming agent may be any agent or combination of agents which enables the sustained release of the at least one active agent from the stearin excipient, with the proviso that when the at least one active agent is a GnRH agonist(s) the pore-forming agent is not lecithin.

Preferably, the pore-forming agent or agents is/are selected from water-soluble agents such as inorganic salts (e.g. chlorides, phosphates and sulphates), organic salts (e.g. acetates, formates, propionates, glutamates, and aspartates), sugars (e.g. glucose, trehalose, mannose, galactose, sucrose and low molecular weight carbohydrates such as hydroxy propyl methylcellulose (HPMC) and carboxy methylcellulose (CMC)), aminosugars (e.g. glucosamine and galactosamine), amino acids/peptides (e.g. lysine, arginine, glutamic acid, aspartic acid, carnosine and aspartame), water-soluble proteins and water-soluble vitamins (e.g. Vitamin B).

Presently, the most preferred pore-forming agent is lecithin (except where the at least one active agent is a GnRH agonist(s)) and the amino acid lysine. Lecithin is a mixture of diglycerides of stearic, palmitic and oleic acids linked to the choline ester of phosphoric acid. The efficacy of lecithin as a pore-forming agent in a sustained release formulation comprising deslorelin and stearin is described in International patent application No. PCT/AU96/00370 (WO 97/00693), the entire disclosure of which is incorporated herein by reference.

As will be evident from the examples herein, variation of the identity and/or amount of the pore-forming agent(s) utilised allows for the manipulation of the release profile of the active agent(s) to suit particular therapeutic uses.

The stearin excipient is preferably in a non-crystalline form. Stearin is partially hydrogenated palm oil having, as the principle fatty acids, C16:0(45%) and C18:0(53%). The melting point of stearin is about 60°C. It is believed that the use of stearin as the excipient contributes to the success of the formulations according to the invention, because it appears, surprisingly, to produce only a minimal to mild inflammatory response in a recipient resulting in the encapsulation of the formulation within a thin layer of fibroblasts. It will be appreciated by persons skilled in the art, that alternative formulations comprising excipient(s) with similar characteristics to those included in the formulation defined above in the first aspect may likewise provoke minimal to mild inflammatory responses and consequently be useful for the sustained-release of an active agent(s). Such alternative formulations are to be regarded as falling within the scope of the present invention.

The formulations according to the invention may be for administration to humans and other animals selected from dogs, cats, other domestic animals, and captive wildlife.

Typically, the formulations will release the active agent(s), *in vitro*, into phosphate buffered saline (PBS: pH 7.3, prepared by dissolving 8.00 g of sodium chloride, 1.00 g di-sodium hydrogen phosphate anhydrous, 0.40 g sodium dihydrogen phosphate dihydrate (0.31 g if anydrous), and 0.05 g sodium azide in 1 litre of deionised water), at 37°C at a rate of about 2-350 µg/day for at least 7 days and up to about 2 years.

Further, the formulations will typically exist as a depot formulation for example in the form of free flowing beads or rods which may have been extruded.

Extruded rods may be cut into predetermined lengths for implantation by standard techniques, in a human or other animal. As will be readily appreciated, the length of the rod will determine the rate and dose of the active agent(s). As opposed to implanting longer rods more than one rod can be implanted in each human or other animal. Injection of a suspension of formulated particulate material such as free flowing beads may also deliver the active agent(s) at the desired rate and dose.

Formulations for administration as free flowing beads and/or implants, particularly to dogs, may be produced as follows:

Stearin (supplied as free flowing beads of 1mm or less in diameter made by Vandenberg Foods) and pore-forming agent are mixed. The active agent may then be added and thoroughly mixed into the excipient and pore-forming agent mixture. This material may then be used for injection. Alternatively the mixture can be transferred to the barrel of a ram extruder that has a 1mm nozzle attached and is equilibrated to 55°C (or other temperature sufficient to soften the stearin). After attaching the ram, pressure (40 psi) is applied until the product begins to extrude. At this point the pressure can be backed off and the product allowed to reach 55°C (or other temperature sufficient to soften the stearin). The product may then be extruded at, for example, a rate of 3 g over a 30 second period. The resulting extrudate is then allowed to cool and then broken up and re-extruded through a 1mm nozzle to ensure uniformity of content throughout the mix. The 1mm nozzle may then be replaced with a 2.3mm diameter nozzle and the product extruded (using the same temperature equilibration procedure prior to extrusion). After cooling the long rods produced can be sectioned into lengths of the required weight and the sectioned lengths sterilised by gamma-irradiation.

Alternatively, formulations for administration as bioimplants, particularly for dogs, may be produced by:

Stearin and pore-forming agent are mixed. The active agent may then be added and thoroughly mixed into the excipient and pore-forming agent mixture. The mixture can then be transferred to the barrel of an extruder that has a 2.3 mm nozzle attached and which has been equilibrated to a

temperature sufficient to soften the stearin. The extruder is started and the product begins to extrude and the extrudate is cut to length. The sectioned length can be terminally sterilised.

Further, in preparing formulations according to the present invention, especially where the at least one active agent is a peptide(s), polypeptide(s) or protein(s), it is preferred that the at least one active agent is firstly pre-treated with a process comprising at least two freeze drying steps. Such freeze drying steps may be conducted in accordance with any of the commonly known methods for freeze drying of proteinaceous materials. It is, however, preferred that the active agent(s) be freeze dried from a 5-50 % (more preferably, 5-15 %) (w/w) solution of the active agent(s) in a suitable solvent (e.g. an alcohol solution such as 30% (w/w) ethanol in water). The freeze dried active agent(s) may then be redissolved or homogenised in a suitable solvent (e.g. 25-75% (w/w) in a diluted weak acid solution such as 1-5 % (w/w) acetic acid in water) and subsequently freeze dried again. Thus, the freeze drying of the active agent(s) may comprise the steps of;

(i) forming a 5-50 % (w/w) solution of the active agent(s),

(ii) freeze drying said solution of step (i),

(iii) forming a 25-75% (w/w) solution or homogenate from said freeze dried active agent(s), and

(iv) freeze drying said solution or homogenate of step (iii).

The term "on an active basis" is to be given its usual meaning in the art. That is, it is used to indicate that the % amount (w/w) of peptide agonist or analogue present in a formulation is based on the dry weight of the peptide agonist or analogue.

The terms "comprise", "comprises" and "comprising" as used throughout the specification are intended to refer to the inclusion of a stated step, component or feature or group of steps, components or features with or without the inclusion of a further step, component or feature or group of steps, components or features.

The invention will hereinafter be further described by reference to the following, non-limiting examples and accompanying figures.

Brief description of the accompanying figures:

Figure 1 provides a graph showing average daily *in vitro* release profiles from three 100 mg rods of each of formulations:
(I) 6% deslorelin, 2% lysine and balance stearin; and
(II) 6% deslorelin, 5% lysine and balance stearin.
The graph demonstrates an initial rapid release of the active agent and then continued release extending over a prolonged period (110 days).

Figure 2 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(III) 6% deslorelin, 2% sodium sulphate and balance stearin; and
(IV) 6% deslorelin, 5% sodium sulphate and balance stearin.
The graph demonstrates that a greater initial rapid release of deslorelin (534 µg vs. 438 µg) was achieved using 5% sodium sulphate as the pore-forming agent. After the initial rapid release (finished at about day 10), the rate of release was about 10-2 µg/day for the next 95 days for both formulations.

Figure 3 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(V) 6% deslorelin, 2% hydroxy propyl methylcellulose (HPMC) and balance stearin; and
(VI) 6% deslorelin, 5% hydroxy propyl methylcellulose (HPMC) and balance stearin.

The graph demonstrates that a much greater initial rapid release of deslorelin (685 µg vs. 403 µg) was achieved using 5% HPMC as the pore-forming agent. After the initial rapid release (finished at about day 10), the rate of release was about 10-2 µg/day for the next 95 days for both formulations.

Figure 4 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(VII) 6% deslorelin, 2% glucose and balance stearin; and
(VIII) 6% deslorelin, 5% glucose and balance stearin.
The graph demonstrates that a much greater initial rapid release of deslorelin (790 µg vs. 403 µg) was achieved using 5% glucose as the pore-forming agent. After the initial rapid release (finished at about day 10), the rate of release was about 50-2 µg/day for the next 95 days for both formulations.

Figure 5 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:

(IX) 6% somatostatin, 0% acetate and balance stearin;
(X) 6% somatostatin, 3% acetate and balance stearin;
(XI) 6% somatostatin, 5% lysine and balance stearin; and
(XII) 6% somatostatin, 10% lysine and balance stearin.

The graph demonstrates that a greater initial rapid release of somatostatin was achieved using lysine than sodium acetate as the pore-forming agent. After the initial rapid release (finished at about day 2), the rate of release in all cases slowed and plateaued by day 7.

Figure 6 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(XIII) 6% naltrexone (NX), 0% pore forming agent and balance stearin;
(XIV) 6% naltrexone (NX), 3% acetate and balance stearin;
(XV) 6% naltrexone (NX), 5% lysine and balance stearin; and
(XVI) 6% naltrexone (NX), 10% lysine and balance stearin.

The graph demonstrates that a sustained gradual release of naltrexone was achieved by all formulations over 23 days of testing, although the average daily release was low when no pore-forming agent was included.

Figure 7 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(XVII) 6% lisinopril, 0% sodium acetate and balance stearin;
(XVIII) 6% lisinopril, 3% sodium acetate and balance stearin;
(XIX) 6% lisinopril, 5% lysine and balance stearin; and
(XX) 6% lisinopril, 10% lysine and balance stearin.

The graph demonstrates that following an initial rapid release (finished at about day 1) a sustained gradual release of lisinopril was achieved by all formulations over 25 days of testing, although the average daily release of this period of sustained release was low in the case of formulation XVII (i.e. 0% pore-forming agent).

Figure 8 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of each of formulations:
(XXI) 6% thyrotropin releasing hormone (TRH), 0% acetate and balance stearin;
(XXII) 6% thyrotropin releasing hormone (TRH), 3% acetate and balance stearin;
(XXIII) 6% thyrotropin releasing hormone (TRH), 5% lysine and balance stearin; and

(XXIV) 6% thyrotropin releasing hormone (TRH), 10% lysine and balance stearin.

The graph demonstrates that following a very rapid initial release, a sustained gradual release of TRH was achieved with formulations XXII, XXIII and XXIV over the 28 day period of of testing Where no pore-forming agent was included, no further TRH release was observed after day 1.

Figure 9 provides a graph showing the average daily *in vitro* release profile from three 100 mg rods of formulation:

(XXV) 6% deslorelin, 3% sodium acetate and balance stearin.

The graph demonstrates that sustained release of deslorelin over 110 days was achieved.

Examples:

Formulations comprising deslorelin and lysine

Formulations I and II (detailed above) were prepared as follows:

Stearin (supplied as free flowing beads of 1mm or less in diameter made by Quest International Pty Ltd (Netherlands) and lecithin (supplied as a deep brown viscous syrup from Lucas Myer (Germany) were hand mixed using a spatula in a small beaker. Deslorelin (Bachem, Switzerland) pre-treated by the above described freeze drying process, was then added and thoroughly mixed into the excipients. The mixed material was transferred to the barrel of a ram extruder that has a 1mm nozzle attached and is equilibrated to 55°C. The ram extrusion pressure was 40psi. The ram was attached and pressure applied until the product began to extrude. At this point the pressure was backed off and the product allowed to reach 55°C. The product was then extruded at a rate of 3g over a 30 second period. The resulting exudate was allowed to cool and then broken up and re-extruded through a 1mm nozzle. This step was included to ensure uniformity of content throughout the matrix. The 1mm nozzle was then replaced with a 2.3mm diameter nozzle. The same product temperature equilibration procedure was conducted prior to extrusion. The product was then extruded and after cooling the long rods produced were sectioned into lengths of the required weight.

Figure 1 provides results of *in vitro* deslorelin release with 100 mg rods containing 6 mg deslorelin. The assay involved immersing each rod into separate containers with 1ml of phosphate buffered saline (PBS; as

hereinbefore described) placed in a reciprocating water bath at 37°C. The PBS was replaced daily and the withdrawn PBS assayed for deslorelin with HPLC. The figure shows that after an initial rapid release of deslorelin, sustained release extending over a prolonged period (110 days) was achieved. The average daily rate of deslorelin release during the sustained release period was within the range 50-2 μg/day.

Formulations comprising deslorelin and sodium sulphate

Formulations III and IV were prepared with sodium sulphate (Ajax Chemicals, USA) as the pore-forming agent in the same manner as described above for deslorelin/lysine formulations.

Figure 2 provides results of *in vitro* deslorelin release with 100mg rods containing 6 mg deslorelin. The figure shows that a greater initial rapid release of deslorelin (534 μg vs. 438 μg) was achieved using a 5% concentration of sodium sulphate rather than a 2% concentration. After the initial rapid release (finished at about day 10), the rate of release was about 10-2 μg/day for the next 95 days for both formulations.

Formulations comprising deslorelin and HPMC

Formulations V and VI were prepared with hydroxy propyl methylcellulose (HPMC) as the pore-forming agent in the same manner as described above for deslorelin/lysine formulations.

Figure 3 provides results of *in vitro* deslorelin release with 100 mg rods containing 6 mg desloelin. The figure shows that a much greater initial rapid release of deslorelin (685 μg vs. 403 μg) was achieved using 5% HPMC rather than 2% HPMC. After the initial rapid release (finished at about day 10), the rate of release was about 10-2 μg/day for the next 95 days for both formulations.

Formulations comprising deslorelin and glucose

Formulations VII and VIII were prepared with glucose (Ajax Chemicals, USA) as the pore-forming agent in the same manner as described above for deslorelin/lysine formulations.

Figure 4 provides results of *in vitro* deslorelin release with 100mg rods, containing 6 mg deslorelin. The figure shows that a much greater initial rapid release of deslorelin (790 μg vs. 403 μg) was achieved using 5% glucose rather than 2% glucose as the pore-forming agent. After the initial rapid release (finished at about day 10), the rate of release was about 50-2 μg/day for the next 95 days for both formulations.

Formulations comprising somatostatin and sodium acetate or lysine

Formulations IX to XII were prepared with sodium acetate or lysine as the pore-forming agent in a manner similar to that described above for deslorelin/lysine formulations. The somatostatin was obtained from Bachem (Switzerland).

Figure 5 provides results of *in vitro* somatostatin release with 100 mg rods, containing 6 mg somatostatin. The figure shows that a greater initial rapid release of somatostatin was achieved using lysine than sodium acetate as the pore-forming agent.

Formulations comprising naltrexone and sodium acetate or lysine

Formulations XIII to XVI were prepared with sodium acetate or lysine as the pore-forming agent in a manner similar to that described above for deslorelin/lysine formulations.

Figure 6 provides results of *in vitro* naltrexone release with 100 mg rods, containing 6 mg deslorelin. The figure shows that a sustained gradual release of naltrexone was achieved by all formulations over 23 days of testing, although the average daily release was low when no pore-forming agent was included.

Formulations comprising lisinopril and sodium acetate or lysine

Formulations XVII to XX were prepared with sodium acetate or lysine as the pore-forming agent in a manner similar to that described above for deslorelin/lysine formulations. The lisinopril was obtained from Sigma Chemical Co. (USA).

Figure 7 provides results of *in vitro* lisinopril release from 100 mg rods, containing 6 mg lisinopril. The figure shows that following an initial rapid release (finished at about day 1) a sustained gradual release of lisinopril was achieved by all formulations over 25 days of testing, although the average daily release of this period of sustained release was low in the case of formulation XVII which contains no pore-forming agent.

Formulations comprising TRH and sodium acetate or lysine

Formulations XXI to XXIV were prepared with sodium acetate or lysine as the pore-forming agent in a manner similar to that described above for deslorelin/lysine formulations. The TRH was obtained from Sigma Chemical Co (USA).

Figure 8 provides results of *in vitro* TRH release from 100 mg rods, containing 6 mg TRH. The figure shows that following a very rapid initial

release, a sustained gradual release of TRH was achieved with formulations XXII, XXIII and XXIV over the 28 day period of of testing Where no pore-forming agent was included, no further TRH release was observed after day 1.

Formulations comprising deslorelin and sodium acetate

Formulation XXV were prepared with sodium acetate as the pore-forming agent in the same manner as described above for deslorelin/lysine formulations.

Figure 9 provides results of *in vitro* deslorelin release with 6mg rods. The figure shows that sustained release of deslorelin over 110 days was achieved.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Claims:

1. A pharmaceutical and/or veterinary formulation comprising about 2-30% (w/w) (on an active basis) of at least one active agent, about 0.5-20.0% (w/w) of a pore-forming agent and the balance stearin, with the proviso that where the at least one active agent is a gonadotropin-releasing hormone (GnRH) agonist(s) the pore-forming agent is not lecithin.

2. A formulation according to claim 1, wherein the formulation comprises about 5-10% (w/w) (on an active basis) of at least one active agent, about 1.0-10.0% (w/w) of a pore-forming agent and the balance stearin.

3. A formulation according to claim 1, wherein the formulation comprises about 5-10% (w/w) (on an active basis) of at least one active agent, about 2.0-5.0% (w/w) of a pore-forming agent and the balance stearin.

4. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from peptides, polypeptides, proteins and nucleic acid compounds and derivatives.

5. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from GnRH agonists.

6. A formulation according to claim 5, wherein the GnRH agonist(s) is selected from deslorelin, eulexin, goserelin, leuprolide, dioxalan derivatives, triptorelin, meterelin, buserelin, histrelin, nafarelin, lutrelin, leuprorelin and LHRH analogues.

7. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from GnRH antagonists

8. A formulation according to claim 7, wherein the GnRH anatgonist is selected from ramorelix, teverelix, cetrorelix, ganirelix, alanex and abarelix.

9. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from somatostatin analogues.

10. A formulation according to claim 9, wherein the somatostatin analogue is selected from somatostatin-14, octreotide, lanreotide and angiopeptin cyclopeptides.

11. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from lipid lowering agents.

12. A formulation according to claim 11, wherein the lipid lowering agent is selected from cerevastatin, mevastatin, simvastatin, pravastatin and lovastatin.

13. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from cyclosporins and cyclosporin analogues.

14. A formulation according to claim 13, wherein the cyclosporin or cyclosporin analogue is cyclosporin A.

15. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from angiotensin converting enzyme inhibitors.

16. A formulation according to claim 15, wherein the angiotensin converting enzyme inhibitor is selected from captopril, enalapril, trandolaprilate, perindoprilate, quinaprilate, fasidotril, omapatrilate and lisinopril.

17. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from calcitonins and calcitonin analogues.

18. A formulation according to claim 17, wherein the calcitonin is selected from human calcitonin, salmon calcitonin and porcine calcitonin.

19. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from substance P antagonists.

20. A formulation according to claim 19, wherein the substance P antagonist is selected from Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2, Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2, Gln-Phe-Phe-Gly-Leu-Met-NH_2, Phe-Phe-Gly-Leu-Met-NH_2, Phe-Gly-Leu-Met-NH_2 and Gly-Leu-Met-NH_2.

21. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from pain killing agents.

22. A formulation according to claim 21, wherein the painkilling agent is selected from morphine, levorphanol, meperidine, bupivacaine, lidocaine, etidocaine and mepivacaine.

23. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from opioid antagonists.

24. A formulation according to claim 23, wherein the opioid antagonist is selected from naltrexone, naloxone and methadone.

25. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from anti-depressant agents.

26. A formulation according to claim 25, wherein the anti-depressant agent is selected from venlafaxine, trifluprom azine, methotrimeprazine, promethazine, buspirone, gepirone and fluoxetine.

27. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from non-steroidal anti-inflammatory agents.

28. A formulation according to claim 27, wherein the at least one active agent is naproxen sodium indomethacin, sulindac, tolmelin, acemetacin, zomepirac, mefenamic acid, fenoprofen, flufenamic acid, phenylbutazone, flurbiprofen, ketoprofen and axsain.

29. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from paroxetine, galanin antagonists, activin, inhibin fragments, adrenocorticotropic hormone (ACTH) and variants and fragments thereof, growth hormone and growth hormone analogues, erythropoietin (EPO) and erythropoietin analogues, endothelin antagonists, leptin and leptin analogues, thyrotropin releasing hormone (TRH) and TRH analogues, theophylline and theophylline analogues.

30. A formulation according to any one of claims 1-3, wherein the at least one active agent is selected from vaccine antigens and DNA encoding vaccine antigens.

31. A formulation according to any one of the preceding claims, wherein the at least one active agent has a log octanol/water partition coefficient (log P) in the range of 5.0 to -3.0.

32. A formulation according to claim 31, wherein the at least one active agent has a log octanol/water partition coefficient (log P) in the range of 3.0 to -3.0.

33. A formulation according to claim 31, wherein the at least one active agent has a log octanol/water partition coefficient (log P) in the range 1.0 to -3.0.

34. A formulation according to any one of the preceding claims, wherein the pore-forming agent is selected from inorganic salts, organic salts, sugars, amino sugars, amino acids, peptides, water-soluble proteins, water-soluble vitamins and combinations thereof.

35. A formulation according to claim 34, wherein the pore-forming agent is selected from lecithin, lysine, sodium sulphate, sodium acetate, glucose and hydroxy propyl methylcellulose (HPMC).

36. A formulation according to any one of the preceding claims, wherein at least one active agent, is released *in vitro* into phosphate buffered saline, as herein before described, at 37°C at a rate of about 2 ug-1.5 mg/day for at least 7 days.

37. A formulation according to any one of the preceding claims, wherein the formulation is in the form of free flowing beads or rods.

38. A formulation according to any one of the preceding claims, wherein the at least one active agent has been pre-treated with a process comprising at least two freeze drying steps.

39. A formulation according to claim 38, wherein the pre-treatment process comprises the steps of;
(i) forming a 5-50 % (w/w) solution of the active agent(s),
(ii) freeze drying said solution of step (i),
(iii) forming a 25-75% (w/w) solution or homogenate from said freeze dried active agent(s), and
(iv) freeze drying said solution or homogenate of step (iii).

40. A method of treating a disease or condition is a human or other animal, the method comprising administering to the human or other animal a formulation according to any one of the preceding claims.

FIGURE 1

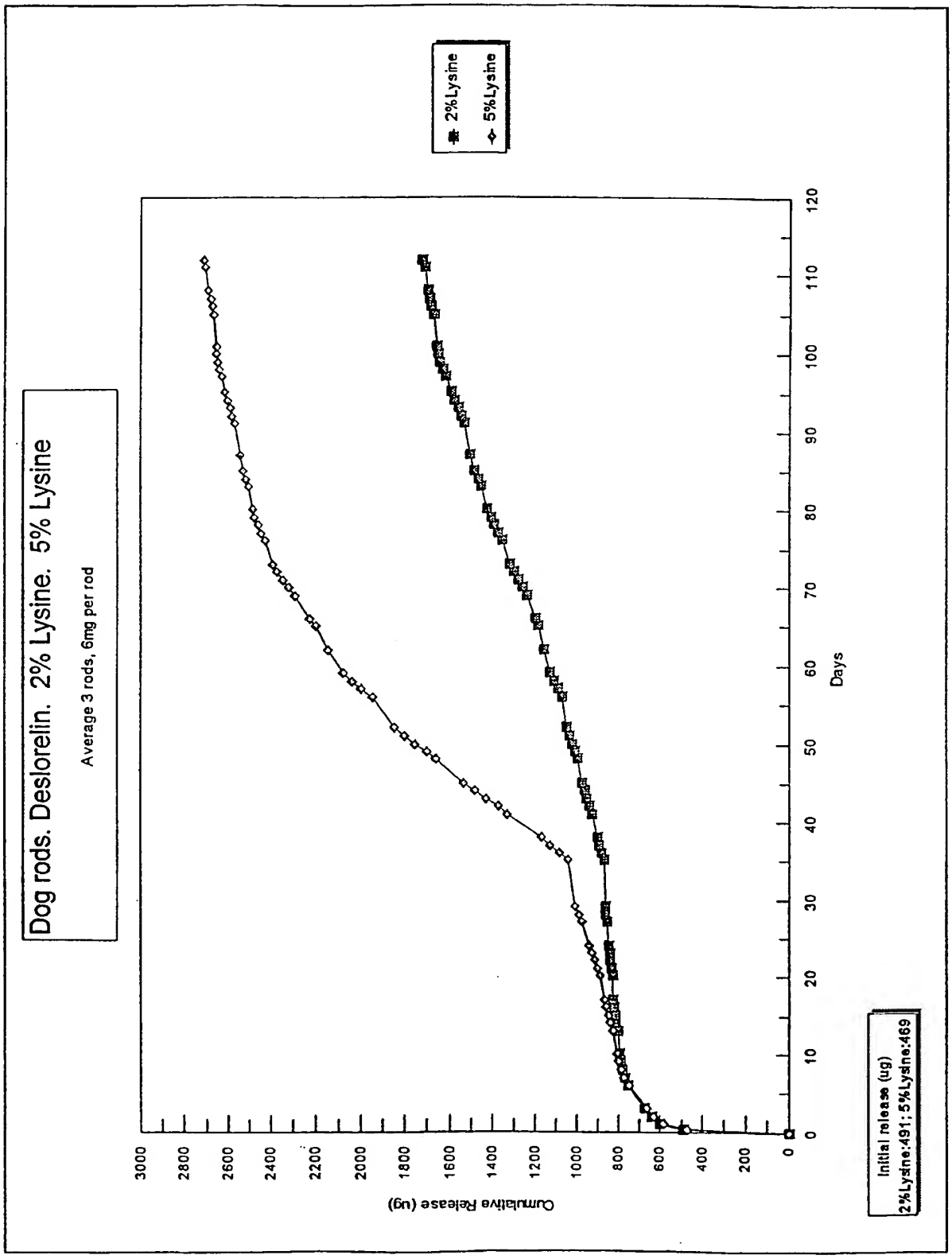

Dog rods. Deslorelin. 2% Lysine. 5% Lysine
Average 3 rods, 6mg per rod
2%Lysine
5%Lysine
Cumulative Release (ug)
Days
Initial release (ug)
2%Lysine:491; 5%Lysine:469

FIGURE 2

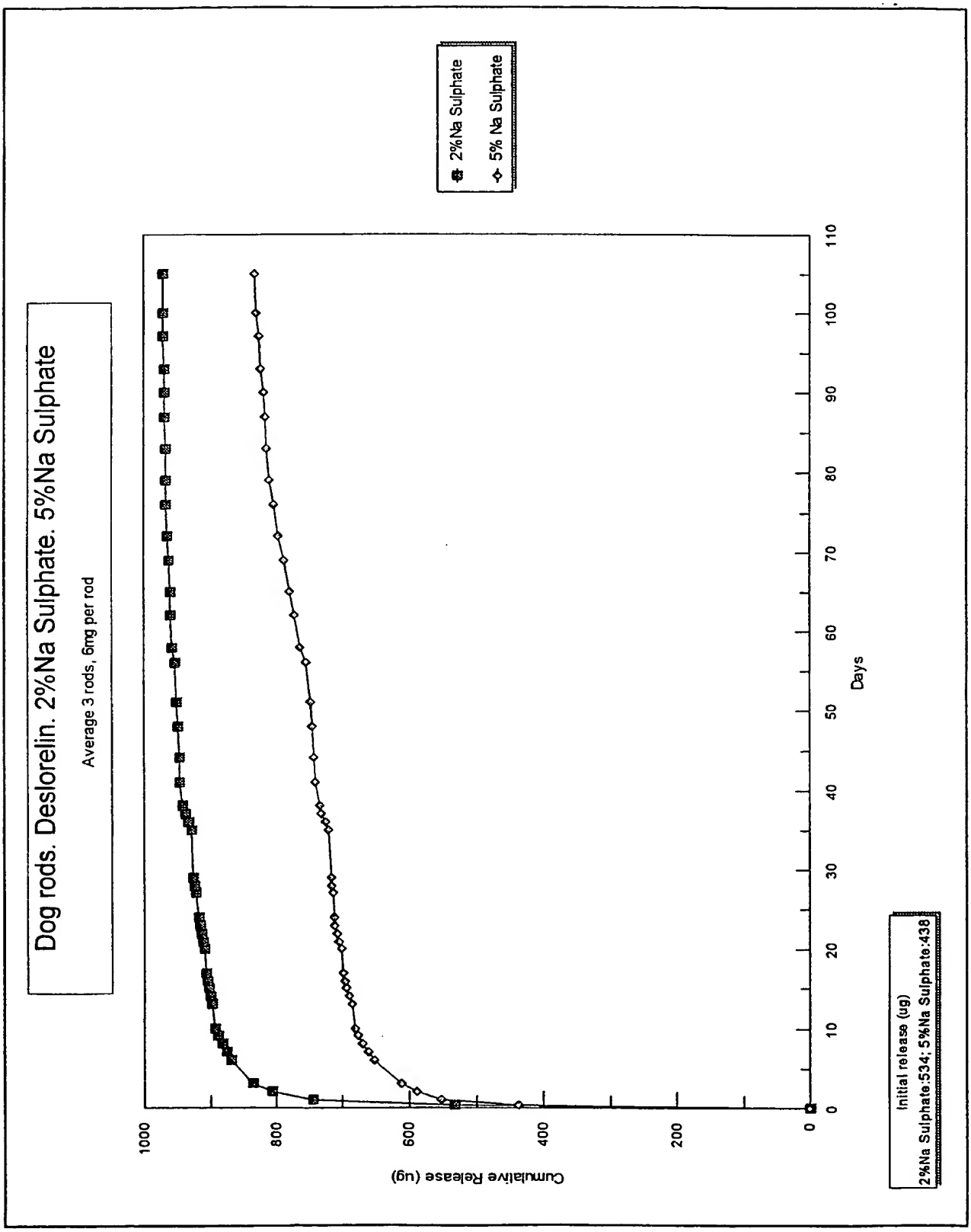

Dog rods. Deslorelin. 2%Na Sulphate. 5%Na Sulphate
Average 3 rods, 6mg per rod
2%Na Sulphate
5% Na Sulphate
Cumulative Release (ug)
Days
0
200
400
600
800
1000
0
10
20
30
40
50
60
70
80
90
100
110
Initial release (ug)
2%Na Sulphate:534; 5%Na Sulphate:438

FIGURE 3

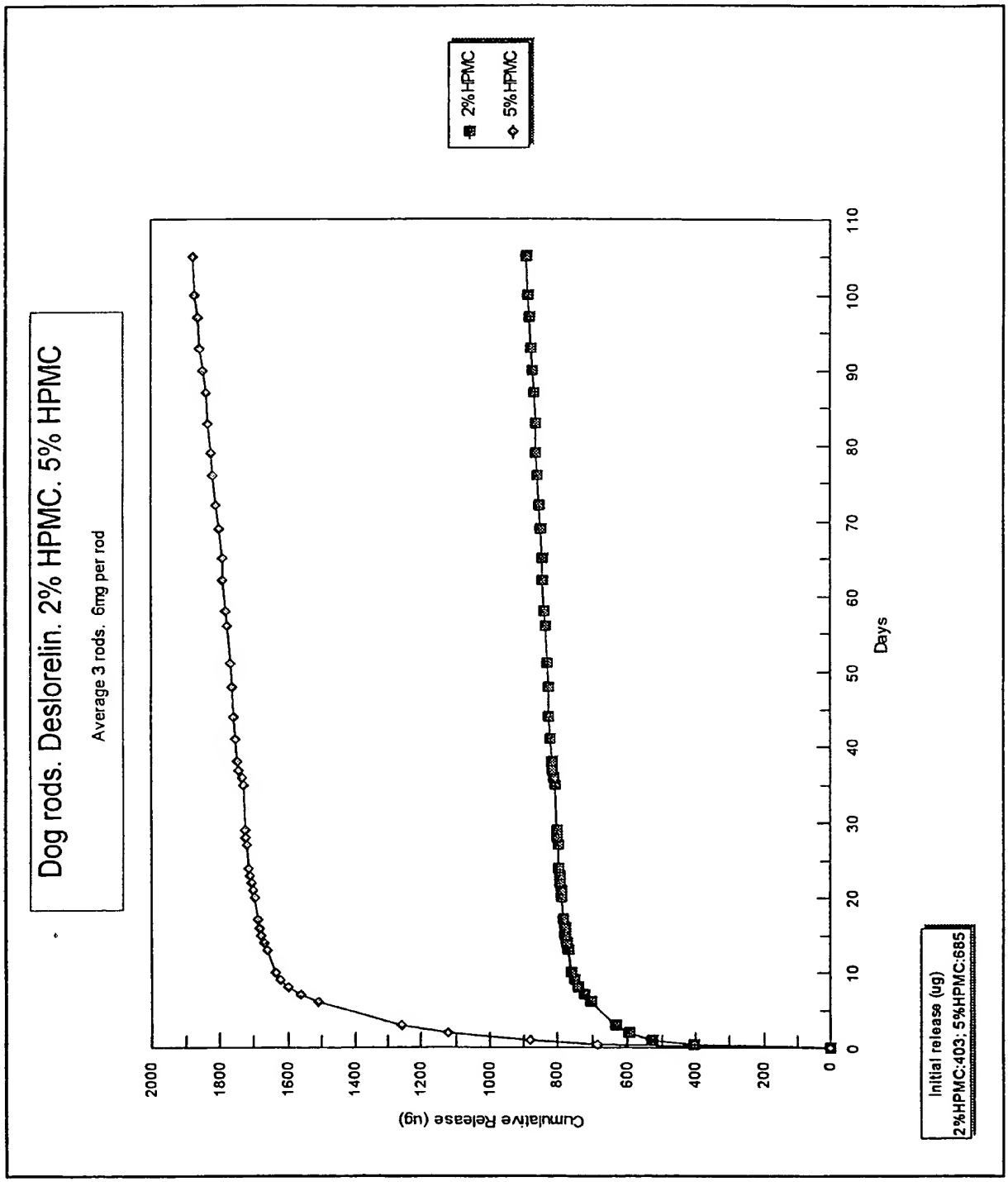

Dog rods. Deslorelin. 2% HPMC. 5% HPMC
Average 3 rods. 6mg per rod
2%HPMC
5%HPMC
Cumulative Release (ug)
Days
Initial release (ug)
2%HPMC:403; 5%HPMC:685

FIGURE 4

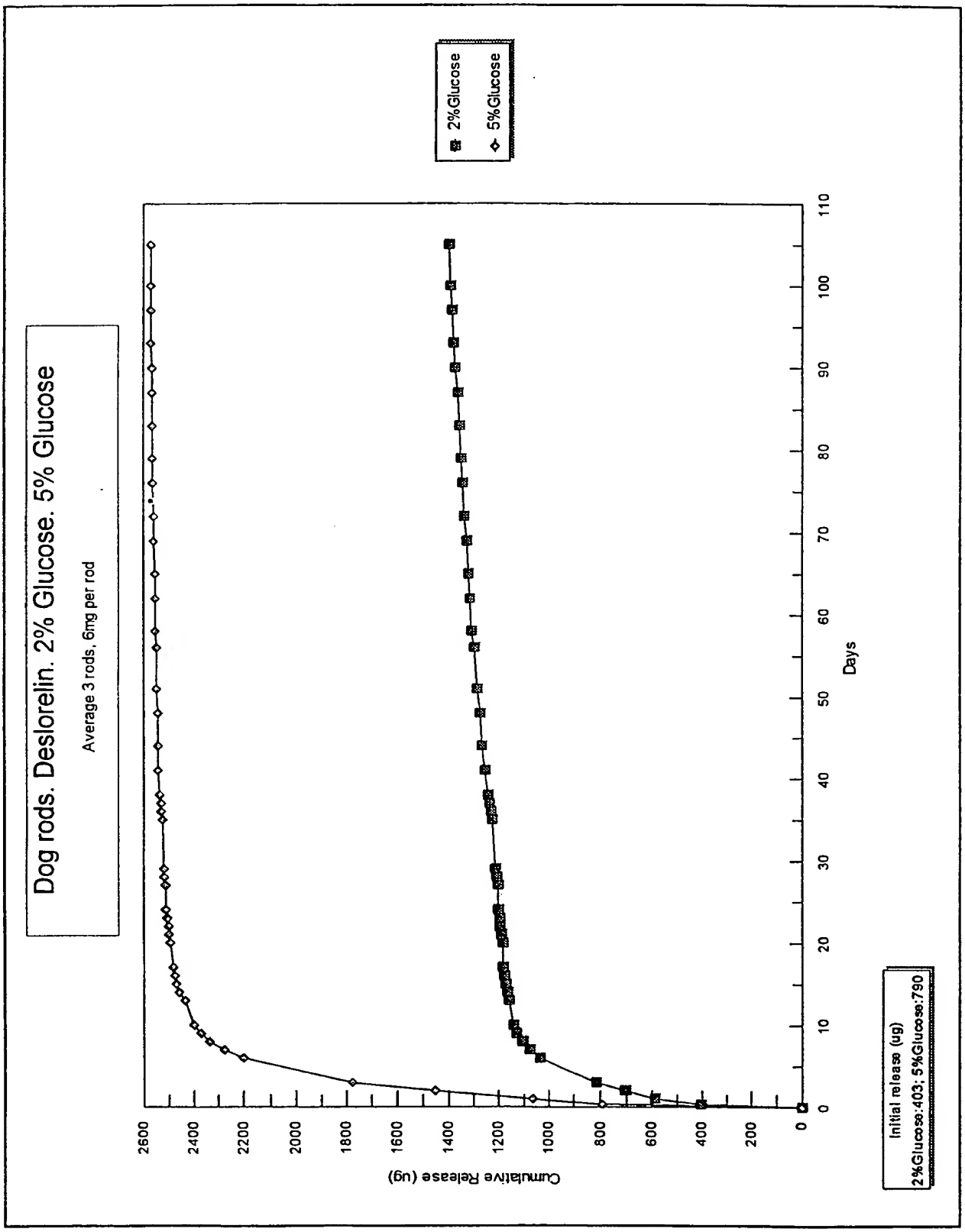

Dog rods. Deslorelin. 2% Glucose. 5% Glucose
Average 3 rods, 6mg per rod
2%Glucose
5%Glucose
Cumulative Release (ug)
Days
Initial release (ug)
2%Glucose:403; 5%Glucose:790

FIGURE 5

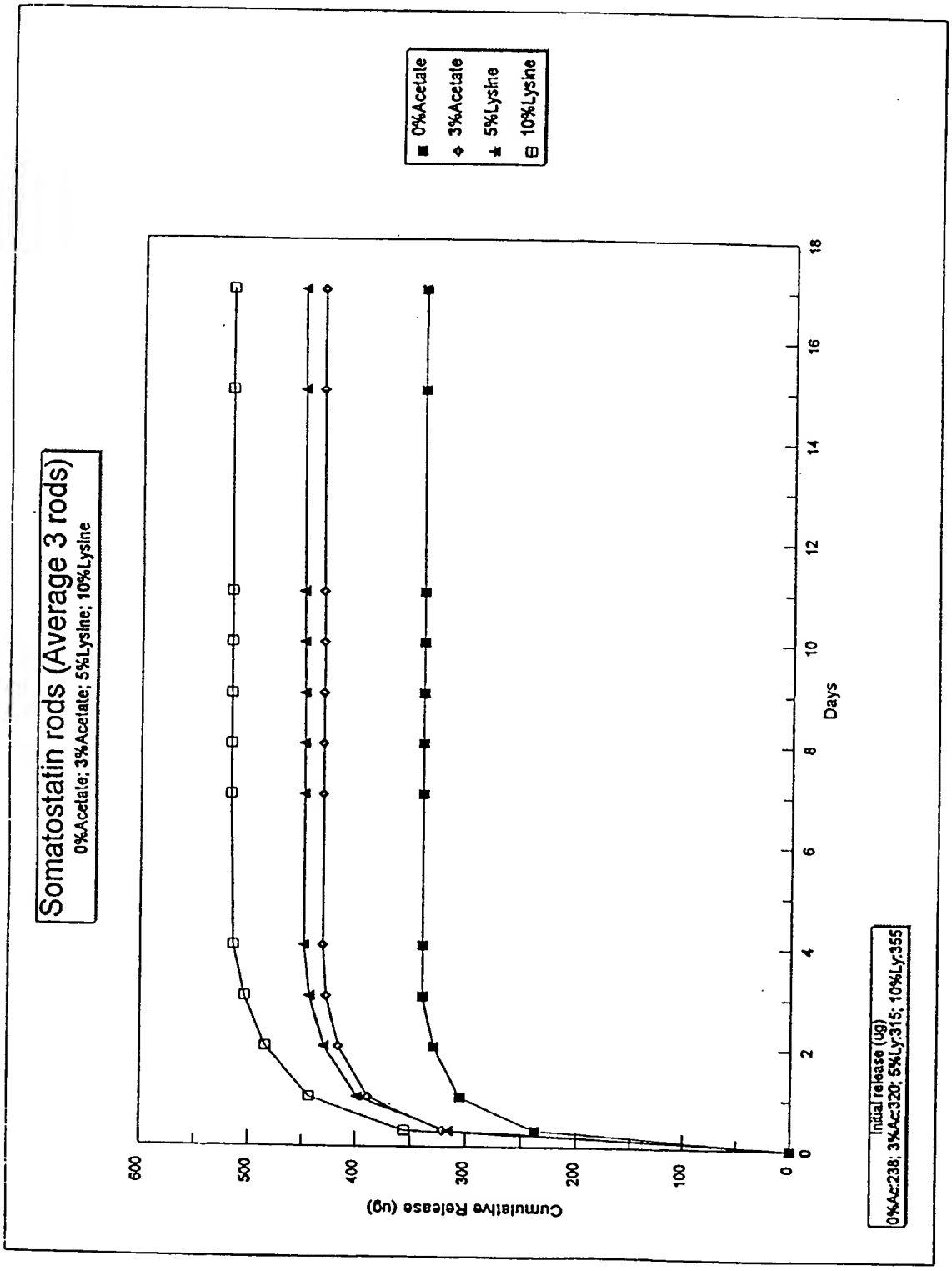

Somatostatin rods (Average 3 rods)
0%Acetate; 3%Acetate; 5%Lysine; 10%Lysine
0%Acetate
3%Acetate
5%Lysine
10%Lysine
Cumulative Release (ug)
Days
0
100
200
300
400
500
600
0
2
4
6
8
10
12
14
16
18
Initial release (ug)
0%Ac:238; 3%Ac:320; 5%Ly:315; 10%Ly:355

FIGURE 6

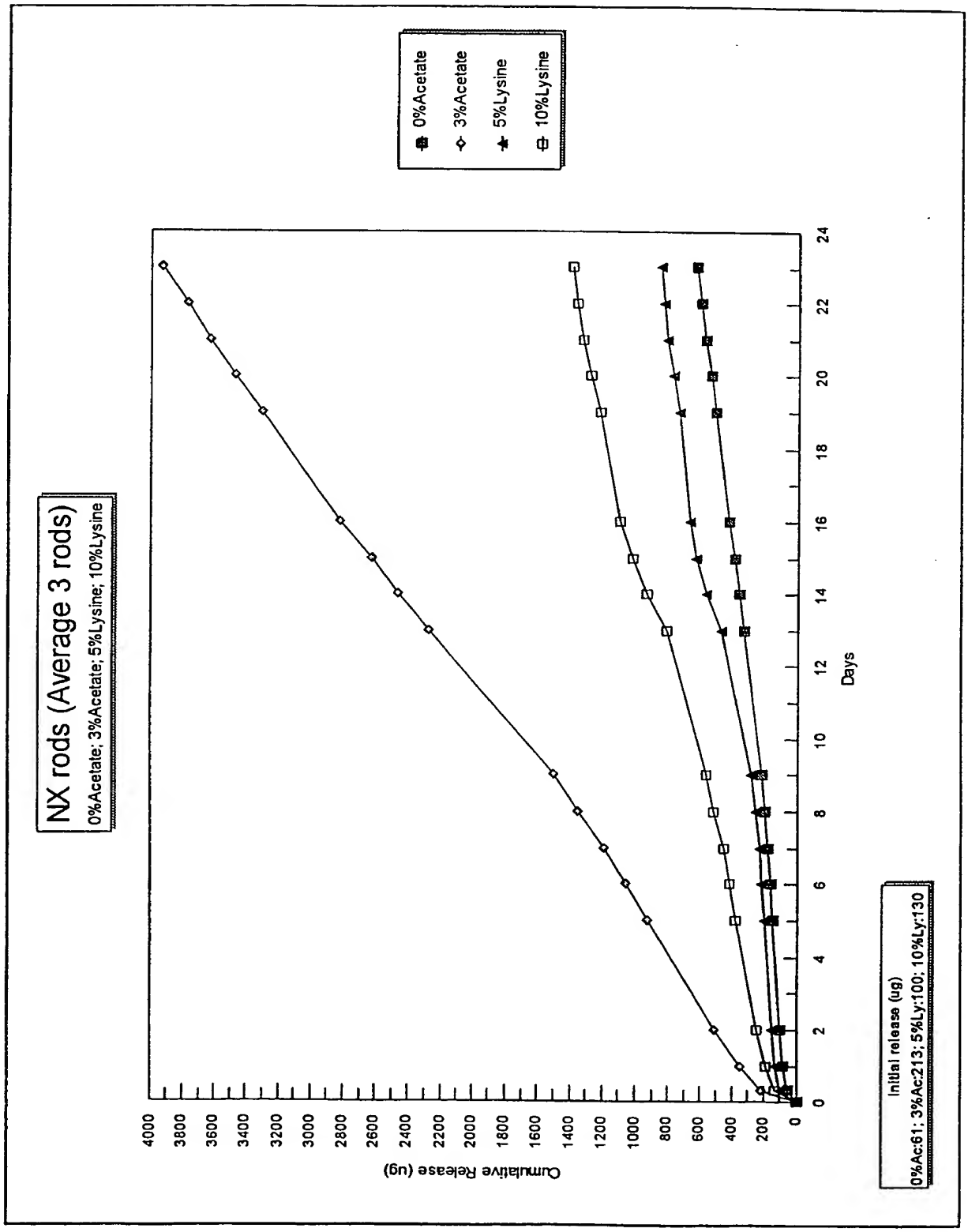

NX rods (Average 3 rods)
0%Acetate; 3%Acetate; 5%Lysine; 10%Lysine
0%Acetate
3%Acetate
5%Lysine
10%Lysine
Cumulative Release (ug)
Days
Initial release (ug)
0%Ac:61; 3%Ac:213; 5%Ly:100; 10%Ly:130

FIGURE 7

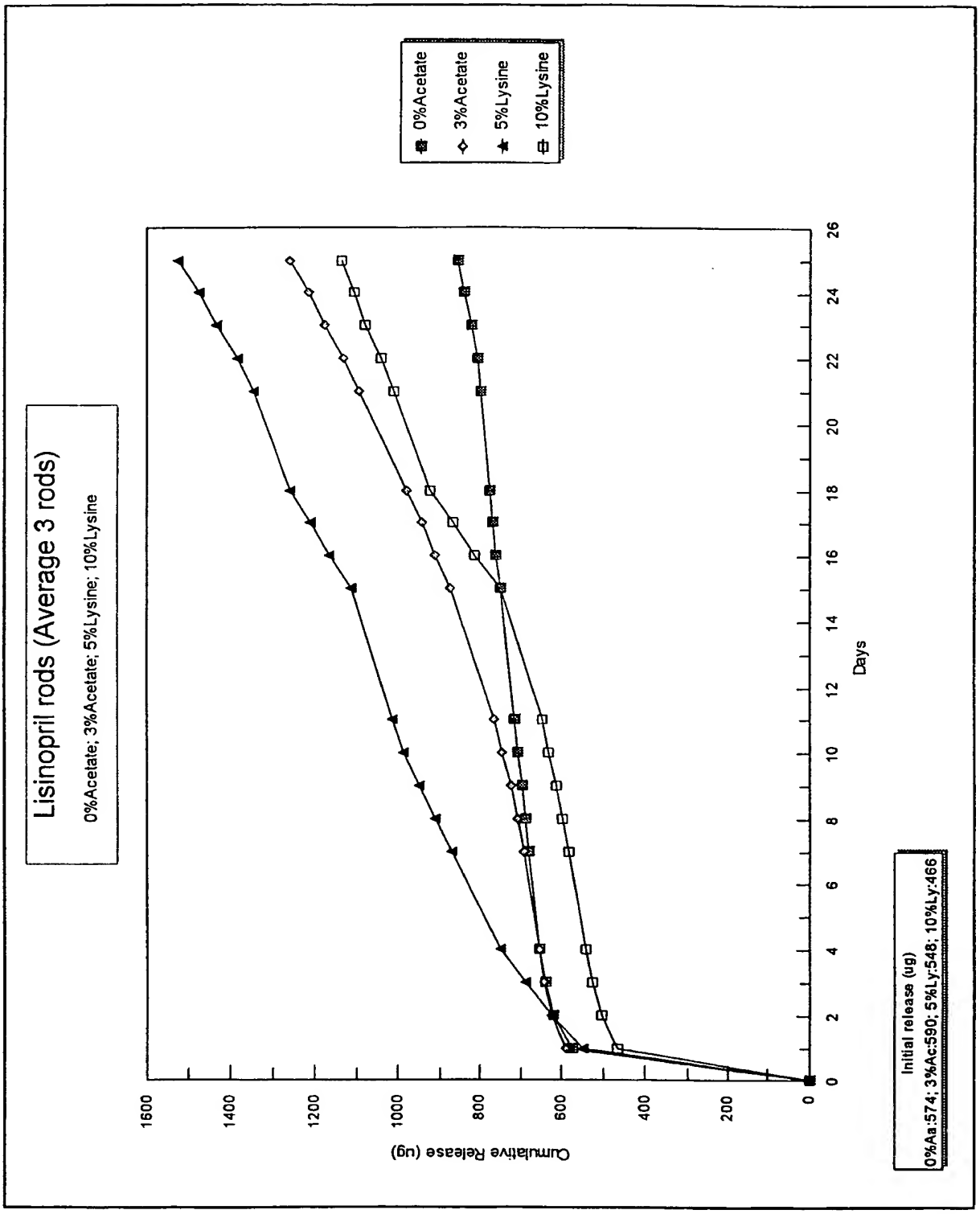

Lisinopril rods (Average 3 rods)
0%Acetate; 3%Acetate; 5%Lysine; 10%Lysine
0%Acetate
3%Acetate
5%Lysine
10%Lysine
Cumulative Release (ug)
Days
Initial release (ug)
0%Aa:574; 3%Ac:590; 5%Ly:548; 10%Ly:466

FIGURE 8

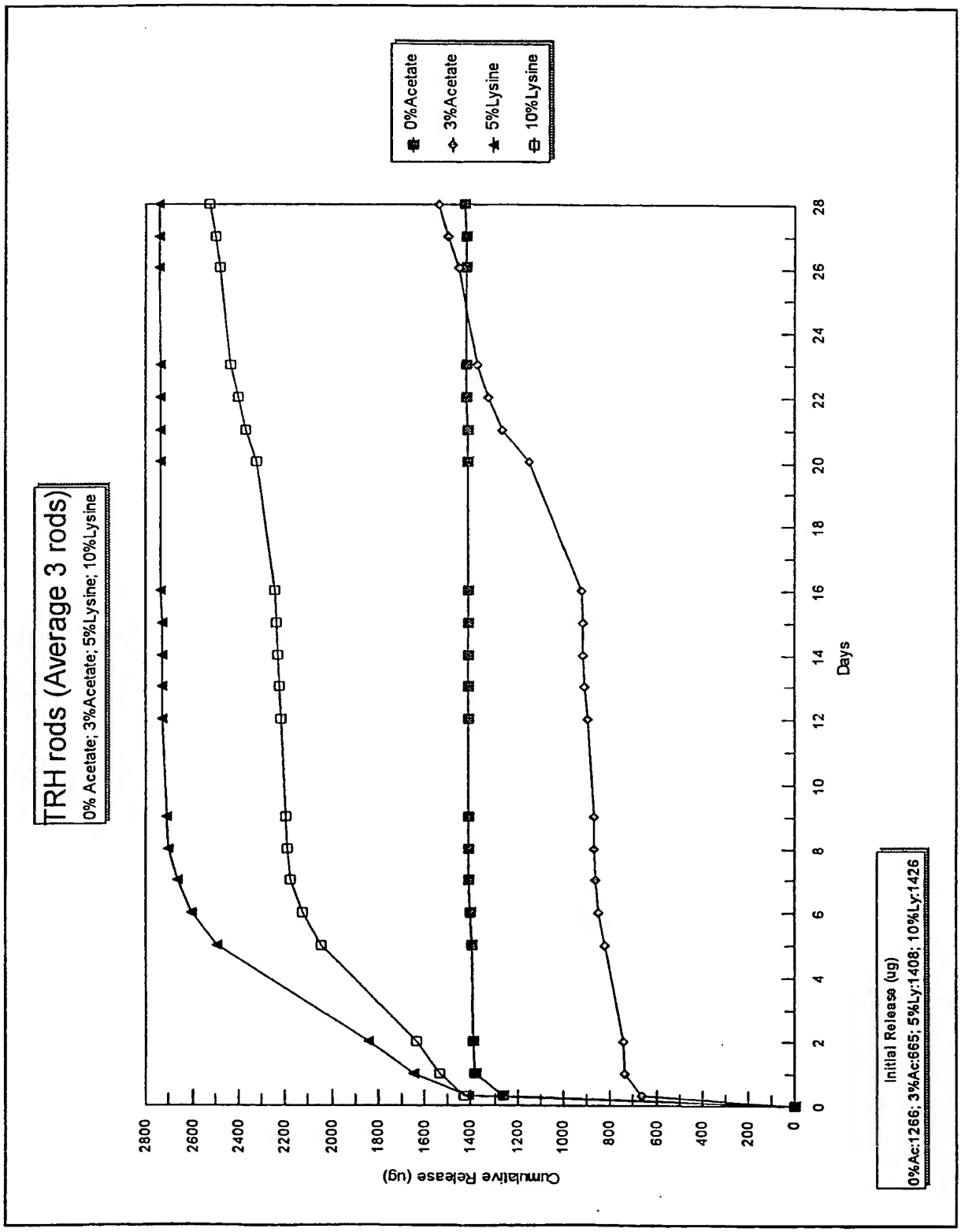
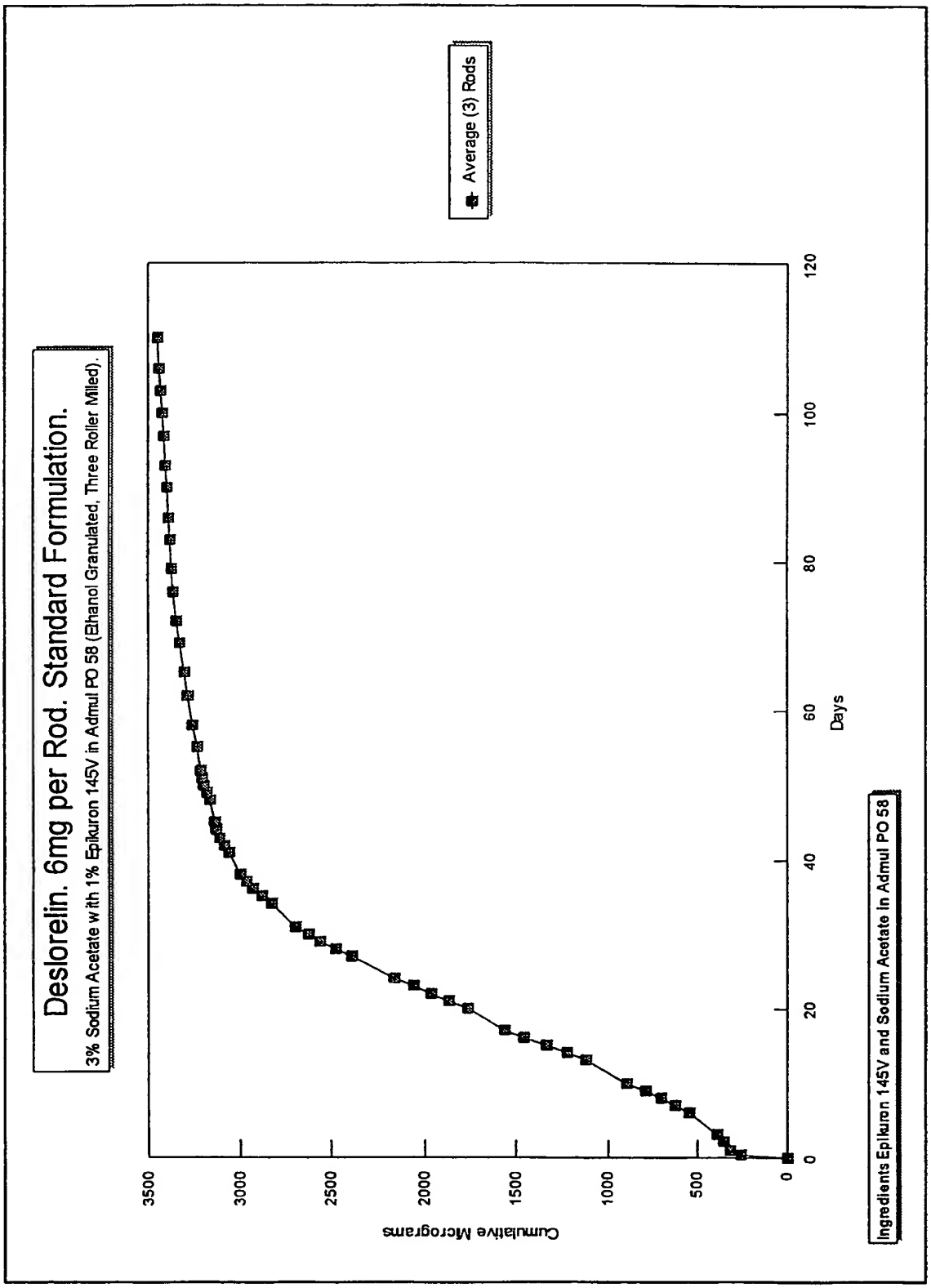

TRH rods (Average 3 rods)
0% Acetate; 3%Acetate; 5%Lysine; 10%Lysine
0%Acetate
3%Acetate
5%Lysine
10%Lysine
Cumulative Release (ug)
Days
Initial Release (ug)
0%Ac:1266; 3%Ac:665; 5%Ly:1408; 10%Ly:1426

FIGURE 9


Deslorelin. 6mg per Rod. Standard Formulation.
3% Sodium Acetate with 1% Epikuron 145V in Admul PO 58 (Ethanol Granulated, Three Roller Milled).
Average (3) Rods
Cumulative Micrograms
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
Days
Ingredients Epikuron 145V and Sodium Acetate in Admul PO 58

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00585

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]:

A61K 31/20, 47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT; .. Glyceryl tristearate; Stearin; excipient; Lecithin
CAPLUS:

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/08623 (F Hoffman-La Roche) 28 April 1994	1-40
Y	WO 97/00693 (Peptide Technology Limited) 9 January 1997	1-40
Y	US 4578391 (Yamanouchi Pharmaceutical Co.) 25 March 1986	1-40

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 1999	- 5 NOV 1999

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200
WODEN ACT 2606 AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No.: (02) 6285 3929

Authorized officer

A. WILCOX
Telephone No.: (02) 6283 2243

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00585

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate. of the relevant passages	Relevant to claim No.
Y	US 5179079 (Novo Nordisk A/S) 12 January 1993	1-40

INTERNATIONAL SEARCH REPORT

Patent Document Cited in Search Report		Patent Family Member					
WO	94/08623	AU	51110/93	CA	2125784	EP	620740
		NZ	256413	US	5863549		
WO	97/00693	AU	59927/96	CA	2225796	EP	871467
		US	5925619	AU	18438/99		
US	4578391	DE	3301638	FR	2519864	AU	18438/99
US	5179079	AU	10858/88	CA	1326210	EP	272097
		NZ	222907	US	5179079	WO	8804556

CONTINUED